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10/748,637	12/30/2003	Nancy L. Brackett	7230-9	6890

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EXAMINER
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SCHUBERG, LAURA J

ART UNIT	PAPER NUMBER
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1657

MAIL DATE	DELIVERY MODE
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06/25/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

Application No.

10/748,637

Applicant(s)

BRACKETT ET AL.

Examiner

Laura Schuberg

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 29 March 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-19 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Response to Arguments***

Applicant's arguments filed 03/29/2007 have been fully considered but they are not persuasive.

Applicant argues that Alexander neither teaches nor discloses methods of increasing sperm motility. Alexander discusses diagnosing CPPS and does not teach treating infertility by contacting a semen sample that contains cytokines with an agent that inactivates or reduces activity of the cytokines. Applicant asserts that the use of an ELISA for detection of cytokines in a semen sample and the binding of antibodies to a highly diluted semen sample does not teach each and every claim limitation of the instant invention. Applicant asserts that detecting and treating are separate entities and antibody types and concentrations used in the Alexander reference would not be useful in increasing sperm motility.

This is not found persuasive because the method of detecting described in the Alexander method includes all the same steps as claimed in Applicant's method. While Alexander is performing the steps for a reason different from Applicant's does not negate the fact that those same steps are being carried out. Applicant's claim limitations do not include specific concentrations of sperm, semen, agents or cytokines. In addition, since Applicant does not claim a specific amount of increase in sperm motility, any increase in sperm motility would meet the limitations of the claimed invention. The use of antibodies that specifically bind to the cytokines in the semen such as  $\text{TNF}\alpha$ ,  $\text{IL1}\beta$ ,

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and IL6 is taught by Alexander (column 11 line 10), and these are the same types as claimed by Applicant. The increased cytokine levels in the semen, which inherently impairs fertility (as taught by Applicant page 5 lines 1-5), would be bound by the antibodies administered by Alexander and would therefore have the same inherent effect as claimed by Applicant in increasing sperm motility (to some degree). The fact that Alexander also discusses other treatments and uses for administration of antibodies does not negate the fact that Alexander, in the performing of the ELISA, has inherently practiced Applicant's invention by performing each of the steps of the method as claimed.

Applicant argues, with regard to Alexander as used in the 103 rejection, that the significance and role of elevated cytokines in Alexander's invention is directed to markers of a completely different disease. Applicant asserts that Alexander neither teaches nor discloses treating the seminal plasma is helpful in treating any disease.

This is not found persuasive because Alexander specifically states that treatment of men determined to be suffering from a disorder associated with elevated levels of one or more cytokines in components or fractions of semen, preferably seminal plasma, comprising administering anti-cytokine agents, such as ant-TNF-alpha agents is provided by the method (column 7 lines 30-36). Although Alexander's invention has been described with regard to preferred embodiments, "it should be understood that various modifications will become apparent to those of skill in the art upon review of the present disclosure" (column 51 lines 8-11). Therefore, Alexander is clearly

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contemplating treating other diseases that are related to elevated levels of cytokines in seminal plasma.

Applicant argues that combining Gruschwitz with Alexander does not result in the instant invention. Applicant asserts that Gruschwitz discusses a myriad of conflicting data and is directed to urogenital infections, which would result in an inflammatory immune response.

This is not found persuasive because Gruschwitz teaches a connection between patients with increased levels of  $TNF\alpha$ ,  $IL1\beta$ , and  $IL6$  and reduced sperm motility (page 162 column 2 lines 17-20) and because the method of Alexander provides for treating men determined to be suffering from a disorder associated with elevated levels of one or more cytokines in one or more components or fractions of semen comprising administering one or more ant-cytokine agents (column 7 line 35). If these increased levels of cytokines decrease motility of sperm as suggested by Gruschwitz, then treatment addressing those increased levels would make the administration of Alexander's method an obvious choice.

Applicant argues that research has shown no evidence of chronic prostatitis in SCI men, the very subjects from which the semen samples were obtained.

This is not found persuasive because Alexander specifically states that the disclosed method is not limited to the preferred embodiments (column 51). Therefore, the method is not limited to the treatment of chronic prostatitis, only to those disorders that are related to elevated cytokine levels in the seminal plasma.

Applicant argues that Angelopoulos does not cure the deficiencies of Alexander in view Gruschwitz. Applicant asserts that Angelopoulos is limited to the effects of tissue culture versus addition of pentoxifylline and 2-deoxyadenosine on non-motile sperm in testicular biopsies of azoospermic men. Applicant asserts that Angelopoulos did not study cytokines or seminal plasma or anticytokine agents and that Angelopoulos is directed to the occurrence of a non-pathological condition.

This is not found persuasive because Angelopoulos teaches that ISCI ( an infertility treatment for males) benefits from enhancement of sperm motility and that there are several alternatives for accomplishing this (page 240). Angelopoulos is relevant in that male infertility in general and sperm motility specifically, can also be addressed by direct ( *in vitro*) treatment of a sperm sample with agents that enhance sperm motility.

Applicant argues that Brackett does not teach or disclose that sperm may be treated with anticytokine agents to increase sperm motility. Applicant asserts that substituting Brackett for Alexander's systemic treatment of a disease is not an obvious leap to make for one of ordinary skill in the art. Applicant asserts that Alexander would teach away from directly treating the seminal plasma. Applicant asserts that there is no teaching as to the amounts, types of antibodies, or that motility would be affected.

This is not found persuasive because Brackett teaches that men with SCI and leukocytospermia have cytotoxic levels of cytokines (p.1227). This teaching would qualify these disorders as suitable for anti-cytokine treatment as disclosed by Alexander. Also, Alexander does not teach that the method is limited to systemic

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administration and specifically states that modifications can be made to the method, therefore Alexander does not teach away from directly treating seminal plasma. Since Applicant has not claimed specific amounts, specific types of antibodies (other than TNF $\alpha$ , IL1 $\beta$ , and IL6) or specific levels of motility, these are not considerations with regard to the patentability of the claimed invention.

Applicant argues that Gerris does not cure the deficiencies of Alexander, in view of Gruschwitz and Angelopoulos. Applicant asserts that Gerris discusses that sperm from the vagina can be retrieved from ICSI. No therapeutic or diagnostic techniques are ascribed to these sperm.

This is not found persuasive because one of ordinary skill in the art would have been motivated to use the method of Alexander to treat semen samples obtained from a woman's reproductive tract because Gerris teaches that this is an excellent alternative for sperm collection for patients who are opposed to masturbation for religious reasons. One of ordinary skill in the art would have had a reasonable expectation of success because this collection method had been used previously for infertility with success (page 213 column 2).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for

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patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

The declaration under 37 CFR 1.132 filed 03/29/2007 is insufficient to overcome the rejection of claims 1-19 based upon 35 USC 102 and 35 USC 103 as set forth in the last Office action because: facts presented are not germane to the rejections at issue and the showing is not commensurate in scope with the claims. The arguments are the same as those provided and addressed above.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5, 6, 8-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Alexander et al (US 6,180,355 B1).

Amended claim 1 is now drawn to a method of increasing motility of sperm by providing from a subject a biological sample comprising sperm and at least one cytokine and contacting the biological sample with an agent that inactivates or reduces the biological activity of the at least one cytokine selected from the group consisting of TNF $\alpha$ , IL1 $\beta$ , and IL6 and increasing motility of sperm.

Claim 2 includes wherein the subject has a condition that impairs fertility.



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Claim 5 includes wherein the sample comprises fluid from the male reproductive tract.

Claim 6 includes wherein the sample comprises semen.

Claims 8-15 include wherein the agent is an antibody that specifically binds to the at least one cytokine.

Alexander teaches the use of sandwich ELISA for cytokines in a semen sample (column 11 line 5). The use of antibodies that specifically bind to the cytokines in the semen such as  $TNF\alpha$ ,  $IL1\beta$ , and  $IL6$  is taught (column 11 line 10) (claims 1, 5, 6, 8-15). The subject's condition causes increased cytokine levels in the semen, which inherently impairs fertility (as taught by Applicant page 5 lines 1-5).

Since Alexander is explicitly practicing all the steps of Applicant's method as claimed by administering cytokine antibodies that specifically bind to the claimed cytokines in a semen sample, Alexander anticipates Applicant's claimed method.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 5, 6, 8-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (US 6,180,355 B1) in view of Gruschwitz et al (Journal of Andrology 1996) and Angelopoulos et al (Fertility and Sterility 1999).

Claims 1, 2, 5, 6 and 8-15 are drawn to the method as described above.

Claims 16-19 include wherein the agent is a soluble cytokine receptor that specifically binds to the at least one cytokine, TNF $\alpha$ , IL1 $\beta$ , and IL6.

Alexander teaches a method that provides for treating men determined to be suffering from a disorder associated with elevated levels of one or more cytokines in one or more components or fractions of semen comprising administering one or more ant-cytokine agents (column 7 line 35). Alexander teaches that compounds that interfere with the production and/or activity of various cytokines are widely known and that such compounds may bind to the cytokine or its receptor, thereby preventing the natural cytokine-receptor interaction (column 7-8). The use of antibodies that specifically bind to the cytokines such as TNF $\alpha$ , IL1 $\beta$ , and IL6 is taught (column 11 line 10) as well as the use of soluble cytokine receptors that bind to the cytokines TNF $\alpha$ , IL1 $\beta$ , and IL6 (column 29, US 5,770,401). Alexander also teaches that various modifications would become apparent to those of skill in the art upon review of reference's disclosure (column 51 lines 8-13).

Alexander does not specifically teach treating infertility by contacting a semen sample that contains cytokines with an agent that inactivates or reduces the activity of the cytokines.

Gruschwitz teaches that patients exhibiting increased levels of TNF $\alpha$ , IL1 $\beta$ , and IL6 showed a significantly reduced amount of progressively motile spermatozoa (page 162 column 2 lines 17-20). These cytokines may result in decreased sperm motility and therefore in reduced ova-penetrating properties (page 162 column 2 lines 42-47).

Angelopoulos teaches a method for enhancing sperm motility that is an alternative to applying motility stimulants for intracytoplasmic sperm injection (page 240). Angelopoulos also teaches the advantages and disadvantages of the different methods of enhancing sperm motility of a semen specimen (page 243, column 1, 2<sup>nd</sup> paragraph).

One of ordinary skill in the art would have been motivated to use the method of Alexander as a treatment for infertile males because Gruschwitz teaches a connection between patients with increased levels of TNF $\alpha$ , IL1 $\beta$ , and IL6 and reduced sperm motility (page 162 column 2 lines 17-20) and because the method of Alexander provides for treating men determined to be suffering from a disorder associated with elevated levels of one or more cytokines in one or more components or fractions of semen comprising administering one or more ant-cytokine agents (column 7 line 35). One of ordinary skill in the art would have been motivated to use the method of Alexander directly on semen samples, such as in intracytoplasmic sperm injection (ISCI-which is a treatment for male infertility) because Angelopoulos teaches that ISCI benefits from

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enhancement of sperm motility and that there are several alternatives for accomplishing this (page 240). In addition, treatment of a sperm sample would be an obvious alternative to directly injecting the agent into the patient (such as taught by Alexander) where fertilization was to be accomplished by alternative methods that require collection of the semen sample prior to fertilization (such as ISCI). One of ordinary skill in the art would have had a reasonable expectation of success because Alexander teaches that compounds that interfere with the production and/or activity of various cytokines are widely known and that such compounds may bind to the cytokine or its receptor, thereby preventing the natural cytokine-receptor interaction (column 7-8).

Therefore, the combined teachings of Alexander, Gruschwitz and Angelopoulos render obvious Applicant's invention as claimed.

Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (US 6,180,355 B1), Gruschwitz et al (Journal of Andrology 1996) and Angelopoulos et al (Fertility and Sterility 1999) as applied to claims 1, 2, 5, 6, and 8-19 above, and further in view of Brackett et al (Physical Therapy 1996).

Claims 1- 6, 8-19 are drawn to the method as described above.

The combined teachings of Alexander, Gruschwitz and Angelopoulos provide the method of claims 1, 2, 5, 6, 8-19 as described above, but do not teach wherein the subject has leukocytospermia or an SCI. However, Alexander does teach that the method may be used to treat conditions associated with elevated levels of a cytokine,

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such as TNF $\alpha$  (column 5 line 12) and that there is a connection between leukospermia and levels of IL-6 (references cited, Shimoya et al).

Brackett teaches that leukocytospermia is observed in many men with SCI and that this condition is thought to contribute to poor semen quality because studies indicate an association with reductions in sperm motility and loss of sperm function as a result of cytotoxic cytokines (page 1227 column 1, 2<sup>nd</sup> paragraph).

One of ordinary skill in the art would have been motivated to use the method of Alexander to treat men with SCI and leukocytospermia because Alexander teaches that the method can be used to treat conditions associated with elevated levels of a cytokine (column 5 line 12) and Brackett teaches that men with SCI and leukocytospermia have cytotoxic levels of cytokines (p.1227). In addition, treatment of a sperm sample would be an obvious alternative to directly injecting the agent into the patient (such as taught by Alexander) where fertilization was to be accomplished by alternative methods that require collection of the semen sample prior to fertilization (such as with spinal cord injured patients). One of ordinary skill in the art would have had a reasonable expectation of success because Alexander teaches the use of anti-cytokine compounds for IL-6 and also that there is a connection between IL-6 and leukospermia (also known as leukocytospermia).

Therefore, the combined teachings of Alexander, Gruschwitz, Angelopoulos and Brackett render obvious Applicant's invention as claimed.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (US 6,180,355 B1), Gruschwitz et al (Journal of Andrology 1996) and Angelopoulos et al (Fertility and Sterility 1999) as applied to claims 1, 2, 5, 6, and 8-19 above, and further in view of Gerris (European Society of Human Reproduction and Embryology 1999).

Claims 1, 2, 5, 6 and 8-19 are drawn to the method as described above.

Claim 7 is drawn to the method of claim 1 wherein the biological sample comprises a fluid produced by the female reproductive tract.

The combined teachings of Alexander, Gruschwitz and Angelopoulos provide the method of claims 1, 2, 5, 6, 8-19 as described above, but does not include wherein the biological sample comprises a fluid produced by the female reproductive tract. However, Alexander does teach that the method may be used to treat conditions associated with elevated levels of a cytokine, such as TNF $\alpha$  (column 5 line 12). Angelopoulos teaches that there are several different methods for treating sperm motility of specimen as described above.

Gerris teaches that although the standard method for collection of a sperm sample is by masturbation, other approaches have been described and assessed. The use of spermatozoa obtained from the vagina or the cervix after full coitus has been suggested for use in ICSI in patients who wish to avoid masturbation for religious reasons and has been described as an excellent alternative to masturbation (page 213 column 2).

One of ordinary skill in the art would have been motivated to use the method of Alexander to treat semen samples obtained from a woman's reproductive tract because Gerris teaches that this is an excellent alternative for sperm collection for patients who are opposed to masturbation for religious reasons. One of ordinary skill in the art would have had a reasonable expectation of success because this collection method had been used previously for infertility with success (page 213 column 2).

Therefore, the combined teachings of Alexander, Gruschwitz, Angelopoulos, and Gerris render obvious Applicant's invention as claimed.

### ***Conclusion***

**No claims are allowed.**

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

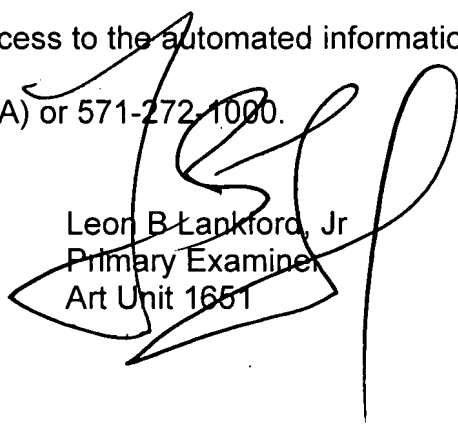
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura Schuberg whose telephone number is 571-272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Leon B. Lankford, Jr.  
Primary Examiner  
Art Unit 1651

Laura Schuberg